STATE MEDICAID P&T COMMITTEE MEETING

THURSDAY, November 13, 2008
7:00 a.m. to 8:30 a.m.
Cannon Health Building
Room 114

MINUTES

Committee Members Present:

Kort DeLost, R.Ph.
Duane Parke, R.Ph.
Karen Gunning, Pharm D.
Raymond Ward, M.D.
Howard Weeks, M.D.
David Harris, M.D.
Matthew Rondina, M.D.
Koby Taylor, Pharm D.
Jerome Wohleb, Pharm D.

Dept. of Health/Div. of Health Care Financing Staff Present:

Jennifer Zeleny, CPhT
Lisa Hulbert, R.Ph.

University of Utah Drug Information Center Staff Present:

Erin Fox, PharmD.
Christina Beckwith, PharmD.

Other Individuals Present:

Don McNaul, Elan	John Steffens, Provider	Bobby White, UCB
Tony Molchan, Abbott	Pam Sardo, Abbott	Linda T. Smith, Biogen Idec
Gary Pettit, Biogen Idec	Eliot Brinton, U of U	Lori Howart, Bayer
Robert Martin, Bayer	Roy Lindfield, Schering-Plough	Ann Gustafson, GSK
Alan Bailey, Pfizer	Laura Gunn, EMD Serono	Ann-Marie Bass, U of U
Ann Schweighardt, U of U	Michael Aluran, Pharmacist	Mona Beckstead, EMD Serono
Derrick Shepherd, U of U	Sarah Ridger, U of U	Brett Brewer, EMD Serono
Sharon Cahoon-Metzger, Biogen Idec		

Meeting conducted by: Karen Gunning, PharmD.

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1. Minutes for October 2008 were reviewed and approved. Duane Parke moved to accept the minutes. Kort Delost seconded the motion. The motion passed with unanimous votes by Koby Taylor, Karen Gunning, Dr. Ward, Dr. Harris, and Kort DeLost.

2. P&T Committee Update: Karen Gunning addressed the Committee. Since July 2007, the Committee has reviewed 19 different drug classes. There has been, since July 1, 2008, an actual savings to the General Fund of $421,000, which is projected to be $1.2 Million. Looking at the total funds saved, which includes the federal matching dollars, there is an actual savings of $1.5 Million and a projected savings of $4.6 Million.

3. DUR Board Update: Tim Morley was not present to give a DUR Board update.

4. Multiple Sclerosis Agents: Christina Beckwith addressed the Committee. The drug review for the disease modifying drugs for multiple sclerosis was prepared by the Oregon Evidence Based Practice Center and published in July 2007. This review included 5 drugs, but 6 different products. The products were glatiremer, or Copaxone; Interferon Beta 1A, which is available as Avonex as an IM injection or Rebif as a Sub Q injection; Interferon Beta 1B, which is Beta Seron; myoxantrone, which is available as Navantrone or generic products; and natalizumab, or Tysabri. The indications differ slightly for the different products, and there have been some changes since the Oregon review. There was a supplemental table that was prepared, which has the current indications as of the end of October. They are all labeled for use in relapsing-remitting multiple sclerosis. Myoxantrone is labeled for use in progressive relapsing multiple sclerosis. In secondary progressive, myoxantrone and interferon Beta 1B are FDA approved; inferferon Beta 1A is recommended for off-label use. In clinically isolated syndrome, Avonex is labeled for use, while Rebif is recommended for off-label. As far as methods for this Oregon review, they developed key clinical questions, and searched key clinical trials that would address those. The key clinical questions were 1.) comparative effectiveness of disease modifying agents in multiple sclerosis, including routes and schedules of administration; 2.) differences in tolerability and safety for these products in multiple sclerosis; 3.) what is the effectiveness of these products in patients with clinically isolated syndrome; and 4.) are there subgroups of patients based on demographics, age, race, ethnic groups, gender, or other medications or comorbidities for which one of these products is more effective or associated with fewer adverse effects. Specific inclusion criteria that were evaluated were adult patients with multiple sclerosis, any of the four subtypes. They also evaluated adult outpatients with clinically isolated syndrome. The effectiveness outcomes for multiple sclerosis or clinically isolates syndrome included disability, clinical exacerbations, quality of life, functional outcomes, and persistence on therapy. For clinically isolated syndrome, they also evaluated progression to diagnosis of multiple sclerosis. They evaluated safety outcomes, and for Interferon Beta products they also evaluated production of neutralizing antibodies. From the literature searches that were conducted, they identified 1880 trials, of these 339 were reviewed, and 168 were included in the review.

   For the first key clinical question on the comparative effectiveness of the products, the focus will be largely on relapsing-remitting MS. This is the largest patient group, and most of the data is in that population. Overall, there are not many head-to-head trials. Looking at relapse-free rates on the Avonex, it is anywhere from 20-48%, for Beta Seron it is 43-51%, Rebif is 56-57%, glatiramer 34-58%, and natalizumab 61-67%. Relapse-free rates have not been evaluated long term for mytoxantrone. These endpoints are not from comparative clinical trials; this is overall from the body of data, and these are endpoints in long term trials. The trials were preferably 2 years, but some were as short as 9 months. As far as percent progression, for Avonex it is 30-54%, for Beta Seron it is 13-33%, Rebif 57%, glatiremer 13%, natalizumab 17-23%, and mytoxantrone 7% based on one trial. As far as head-to-head trials, there were 4 head-to-head trials for the interferons. The Oregon reviewers conducted extensive analysis of placebo trials. Based on two trials, they concluded that Beta Seron was more effective than Avonex for both relapse and progression. The number needed to treat for both endpoints was 6. Based on 2 trials, they concluded that Beta Seron and Rebif were equal in efficacy. Based on 2 trials, they concluded that Rebif

was more effective than Avonex for relapse, but not for progression. For glatiramer, there are no head-to-head trials. This product is better than placebo for relapse, and may be better than placebo for progression. Based on an observational report, interferons and glatiramer are equivalent for most endpoints, although glatiramer may be more effective for annualized relapse rate and discontinuations after 6 months. For natalizumab, there are no head-to-head trials or observational trials; however, this product is better for both relapse and progression than placebo. Mytoxantrone, there are no head-to-head or observational trials, but this products is better than placebo for progression. Relapse has not been assessed. In secondary progressive disease, there are no head-to-head trials, and only the interferons have been studied. There are 5 trials and some indirect analysis. Avonex is at least as effective as placebo, and may be more effective, although the jury is still out based on the lack of overall data. Beta Seron is considered to be more effective than placebo, and Rebif is equivalent to placebo. Relapse-free rates for these products in secondary progressive MS: Avonex is about 74%, Beta Seron trials did not evaluate that, and Rebif relapse-free rates are about 61%. Progression rates have not been evaluated for Avonex in secondary progressive. For Beta Seron, it improved time to progression anywhere from 668 to 981 days compared to placebo, and percent with progression is from 32-50%. For Rebif, time to progression was similar to that seen with placebo, and percent with progression was 41%. In primary progressive MS, there are no head-to-head trials, and only Avonex has been studied. It was equivalent to placebo for time to progression. For progressive relapsing MS there are no trials of any agent. For the mixed populations, there are no head-to-head trials. In patients with relapsing-remitting and secondary progressive, Beta Seron was at least as effective as untreated controlled for quality of life, and patients with the lowest baseline disability saw the greatest benefit. Natalizumab was at least as effective as placebo. It was equivalent to placebo for disability; however, it was more effective than placebo for preventing relapse. Mytoxantrone was more effective for both relapse and progression than placebo. There are no trials of Avonex, Rebif, or glatiramer in this specific mixed population of relapsing-remitting and secondary progressive. For primary progressive and secondary progressive mixed population, glatiramer was at least as effective as placebo for progression and disability; however, this was a different formulation and not the formulation that is currently marketed. There are no trials in this mixed population of interferons, natalizumab, or mytoxantrone.

The second key question was the safety summary of comparative safety. For the interferons in relapsing-remitting MS, they used again the 4 head to head trials and extensive analysis. Based on these, Beta Seron and Avonex are equivalent in safety. Beta Seron and Rebif have not been evaluated for comparative safety. In Avonex vs. Rebif, there were some differences. Flu syndrome was significantly more common in Avonex (53%) than in Rebif (45%). While this was statistically significant, it is not a large difference in the numbers. Injection site reactions, increased liver function tests, and increased white blood cells were more common with Rebif than Avonex. The Oregon reviewers conducted a pooled analysis of all the trials that were available for the interferons, and concluded that there were still some differences in ADRs between these products. For discontinuations due to adverse events, injection site reactions, and fever, Beta Seron was most likely to cause these adverse events and Avonex was less likely. Rebif fell in the middle. Flu syndrome was most common with Avonex, followed by Beta Seron and Rebif. Beta Seron and Rebif were considered equivalent for that adverse event. Fatigue was more common with Rebif

than Beta Seron. Depression was most common with Beta Seron and Avonex, and less common with Rebif. For thyroid dysfunction and increased liver function tests, they found no difference. Overall, the interferons cause more adverse events than placebo. The serious adverse event seen was depression, but they could not assess comparative risk with that. For glatiramer, there were more adverse events for glatiramer than placebo. An observational analysis found that overall rates and discontinuations due to adverse events were similar with glatiramer and the interferons. Natalizumab was no different from control in the available trials. They were unable to compare this product with other products based on available information. As far as serious adverse events, there have been two cases of progressive multifocal leukoencephelopathy. For this reason, this product is indicated for use only as monotherapy, and it also has a restricted distribution system. The analysis of the trials was unable to determine whether these were directly caused by the drug or if there was just an association. Mytoxantrone causes more adverse events than placebo. There are no cases for comparison with the other products. As far as serious adverse events, they include dose-related cardiotoxicity and dose-related acute leukemia. Looking at the interferons causing neutralizing antibodies in relapsing-remitting MS, if these antibodies are present, they may increase relapse rates at 3-4 years. However, even if patients develop these antibodies, 40-50% of patients who get them eventually become antibody negative, even if they continue therapy. Because there are no direct comparisons, the reviewers could not assess comparative risk. The usual time to develop antibodies is a little bit different for the products. With Avonex and Rebif, they usually develop around 9 months, and for Beta Seron they develop after 3 months. The percent of patients developing them varies widely, anywhere from 12-36% for Avonex, 30-40% for Beta Seron, and 2-8.5% for Rebif.

The third question – what is the effectiveness of these products in clinically isolated syndrome? The trials that were evaluated looked at the endpoint of conversion to Multiple Sclerosis. There were no head-to-head trials. For the interferons there were 3 trials and an indirect analysis. With Avonex, 35% converted compared to placebo, which had 50% of patients who converted. Beta Seron was also superior to placebo with 34% of patients converting compared to 45% for placebo. Rebif was also superior to placebo, with 26% converting compared to 44% with placebo. There were no trials for glatiramer, natalizumab, or mytoxantrone for this endpoint.

The fourth key clinical question – are there differences in safety or efficacy in various patient subgroups? There is very limited information, and this is only around the interferons. The reviewers concluded that they could not draw any conclusion around this. There is one post-hoc analysis of African Americans comparing Avonex with Rebif, but the sample size was too small to draw any conclusions. Another meta-analysis and observational studies evaluate pregnancy risk in women. They primarily look at the comparison of interferon versus no interferon, but did not evaluate the differences between these agents. There are no evaluations at all for glatiramer, natalizumab, or mytoxantrone.

Overall, for relapsing-remitting multiple sclerosis, all of these agents are effective. There are few head-to-head trials. For secondary progressive MS, Beta Seron is effective, Avonex may be effective, and there is no evidence suggesting efficacy for the other agents. As far as adverse events, all of these products cause adverse events.

There are few direct evidence-based comparisons, and serious adverse events differ between the classes. Interferons, glatiramer, mytoxantrone, and natalizumab are pharmacologically distinct classes, which explains the difference in the ADRs. The Drug Information Service also sent a comparative table showing the updated indications, shows the differences in dosing and routes of administration. Many of the products are available for self-administration. However natalizumab and myoxantrone require infustion in either a clinic or hospital setting. Dosing frequency varies from daily to once every three months depending on the product. None of these products are labeled for use in children less than 18 years of age. There is also a summary of black box warnings and adverse events, which differ between the agents.

Sharon Cahoon-Metzger, PhD of Biogen Idec addressed the Committee. Biogen Idec has two products for the treatment of MS, Avonex and Tysabri. The objective today is to provide clinical information about Avonex, but she would also answer questions about Tysabri. Biogen Idec positioning in terms of availability of products is that they advocate for open access to all products. It has become increasingly appreciated that MS is a heterogeneous disease or group of diseases. Patients do not respond to all therapies homogeneously. The judgment as to what the most appropriate therapy is should be a clinical judgment and a discussion between the physician and the patient. Avonex is the only one of the agents whose primary endpoint in the phase III study was actually prevention of disability and progression. It achieved that primary endpoint by decreasing progression, sustained over 6 months by 37%. In addition, Avonex is the only one of the agents that has the trifold FDA approved indication of prevention of disability and progression, reduction in relapse rate, and an indication in clinically isolated syndrome. In addition to significant effects on traditional MRI outcomes, within the last year there was a publication by Robert Zevatenoff, et. al studying Avonex on grey matter atrophy. Classically, MS has been viewed as a white matter disease, but it is becoming increasingly appreciated that grey matter is also affected in MS. While it is not easily evaluable on MRI, there are some sites that have more capability to study this on MRI and have been looking at the effect on grey matter. As it turns out, grey matter is affected very early in the disease and is strongly correlated with disability progression. This group was able to demonstrate that Avonex has significant impact on grey matter atrophy over a 3 year period on patients treated with Avonex versus placebo. About 6 weeks ago, they also presented some information at Spectra, the European conference on MS, showing a finding of an Avonex long-term safety study called Assurance. In this study, the patients who are currently on Avonex demonstrated a lower EDFS progression relative to their counterparts not on Avonex, a decreased chance of reaching milestones 4, 6, and 7 on the EDFS progression, they reported increased quality of life, and increased self-sufficiency and independence. About 80% patients had 10 years of exposure to Avonex, with a median exposure of 13 years. There is controversy regarding the interferons in terms of appropriate dose and frequency of dosing. There are a number of studies that have come out recently that actually support a study that Biogen Idec did a number of years ago wherein Avonex was evaluated at the current marketed dose and a double dose, and no difference in efficacy was found. More studies are now coming out that suggest that double doses do not provide increased clinical efficacy, and a number of studies showing parity among the interferons and equality with Copaxone and some of the other DMTs. Adherence and compliance are also important. Avonex is a weekly dose as opposed to some of the other agents, and they

have evidence suggesting that compliance and adherence is greater. Medicaid is respectfully requested to provide equal access to all agents.

Dr. John Foley addressed the Committee. He is the director of Rocky Mountain Neurological and Rocky Mountain Multiple Sclerosis clinic and would like to present the clinician's perspective. He takes care of about 1400 patients with MS. He started practice prior to there really being any agents being available for treatment, so he has the perspective of both sides from when there was just ACTH and Solumedrol available until now. Clearly there has been an enormous difference in what is seen in people coming back on medications. One of the problems is that MS is not necessarily a homogeneous disease. There may actually be different subgroups of people with MS, some that have slightly different immunological make-ups of the plaques that are found in the brain. It is clear from his perspective that there are some people who do better on some agents rather than other agents. It is very difficult at the front end which agents will be optimal or therapeutic. He would like to echo Dr. Cahoon-Metzger in stating that he needs all of these agents to be available to find which therapy will be optimal for an individual. Looking at treated versus non-treated populations, in a non-treated population roughly 50% of people will go on to secondary progressive MS at around 10 years. It is considered important to get going with therapy fairly quickly. It looks like there are 2 phases of MS that coexist, one being the inflammatory phase that can be addressed with these drugs, and a degenerative phase of the disease that cannot be affected directly with any available drugs. In MS, time is brain, and the sooner that the therapy is started to minimize the inflammatory process in the earlier stages of the disease, the patient will do much better in the longer term. He is now taking care of patients out 15 years on these various agents. Therapies are getting better and better. The first generation drugs were a huge advance over ACTH and Solumedrol. This next generation of drugs, including a number of drugs in phase III clinical trials hold the promise to even do better to minimize relapse rates and suppress the progression of disease and disability. He has seen a number of people who were fairly non-functional stabilize, and, in some cases, improve enough that they come off Medicaid and start working again.

Dr. Ward asked if he can get a feeling, based on speaking with a patient, as to which agent they will respond to better. Dr. Foley stated that he cannot. He uses some indicators, such as a very high lesion rate, he will tend to go with an interferon rather than Copaxone, since interferon seems to do better in crossing the blood-brain barrier. Other than that, it is difficult to predict. There is not a good clinical marker that can be used at the front end to determine which agent a patient will respond to. Dr. Ward asked if there would be a big drawback, particularly if Medicaid stands to save a large amount of money, to ask that a physician try one agent first and still have all of the other options available to him. In this case, a physician would still have the option to override the PDL and have his choice of medications. Dr. Foley felt that some system like that could work, as long as there is enough flexibility to understand that there is heterogeneity in the population and that the patient may need to change to another agent.

The Committee asked Dr. Foley what he usually starts with. He has patients on all of the drugs. There are some times that certain drugs work better than others. He probably starts more commonly with the interferon class than any other class, but that

is probably because he gets a lot of patients that have more severe MS, that have more active gadolinium enhancement. Compliance is an issue with injectable agents, that are either IM or SubQ. With the IV agents he is able to monitor compliance because his office administers them. To some degree, it is easier to have a lower weekly dosing schedule, but with education he can usually get patients to be reasonably compliant.

The Committee stated that there is quite a bit of difference in usage between Copaxone and the interferons. Dr. Foley was asked if he can explain that. Glatiramer has about 44% of the market and the interferons have most of the rest. Dr. Foley stated that all clinicians have their own preferences, but he feels that glatiramer poses less challenges in the way of side effects than the interferons, and it is a somewhat easier drug for physicians to start and not have to worry too much about. On the other hand, there are some challenges in the phase III trial with glatiramer and its effect on disability, primarily because of the placebo group. He feels that some variability will be seen, and that glatiramer is probably an easier drug to use from the clinician's standpoint. The more recent data in glatiramer has been more positive in comparative trials.

Karen Gunning asked what a reasonable trial of an MS drug was. Dr. Foley stated that the trend among MS treating physicians is to try to make sure that there are not a lot of relapses during the drug therapy, assuming that the drug has been established for an adequate period of time. He thinks that 6 months is probably an adequate trial. If there are still relapses or MRI lesion progression after 6 months, the therapy needs to be reconsidered. At that point a patient would probably be moved to a drug in another class.

Dr. Ward asked if it is typical for a commercial insurance company to require a certain drug before another one can be prior authorized. Most insurance companies are OK with anything in either the glatiramer or interferon class. There are a few insurance companies that tier it, but in general that class of drugs is not a major issue. When moving to something like Tysabri or Navantrone, there is almost always a requirement to have failed or not tolerated the interferons or glatiramer. Dr. Ward asked if companies tend to have preferred interferons. Insurance companies do tend to have one or two preferred interferons, but they are not uniform across all of the companies.

Karen Gunning stated, as a point of clarification, that because Tysabri and mytoxantrone are administered in the physician's office, they will not be considered for the PDL.

Dr. Laura Gunn, Medical Science Liason for EMD Serono addressed the Committee. She thanked the Committee for allowing her to speak on behalf of Rebif, and stated that like the other companies, EMD Serono advocates for open access for the MS agents. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology is responsible for the article "Disease Modifying Therapies in MS". This report is a review of the published data for each DMD, with an emphasis on the product's pivotal trials and evidence. One of the opening remarks of the review states, "The most important therapeutic aim of any disease modifying therapy in MS is to prevent or postpones long term disability." The article defines

the three efficacy parameters of the trials as 1) delaying the progression of disability as confirmed by EDSS, 2) relapse rate reduction, and 3) prevent a change on MRI. When looking at each of the drugs' pivotal trials, only Rebif had a statistically significant reduction on all three of the efficacy parameters. Patients in the Rebif 44mcg group had 135% relative reduction over placebo in T2 lesion area or burden of disease. There was also a 32% reduction in relapses and 30% fewer patients experienced disability progression. The PRISMS 2-year trial also showed a 54% reduction in the number of steroid courses as well as 52% reduction in hospitalization for patients on the recommended dose of Rebif. While Rebif was approved outside of the US in 1998, it was not allowed to enter the US marketplace because Avonex held orphan drug status. For Rebif to gain entry into the US, EMD Serono undertook the EVIDENCE trial. Based on the results of the EVIDENCE trial, Rebif was allowed to overturn the orphan drug protection that Avonex had and enter the US market in 2002. The was the first time in the over 20 year history of the orphan drug act that status was overturned based on clinical superiority as defined by the FDA. In this head-to-head trial with Avonex, Rebif was shown to be clinically superior in reducing relapses and MRI activity at 24, 48, and 64 weeks. After 64 weeks, patients on Avonex had the opportunity to cross over to Rebif. A majority did so, and the results showed an additional 50% reduction in relapse rate and a 22% reduction in MRI activity in those patients who were initially on Avonex and crossed over to Rebif. Additionally in the EVIDENCE trials, side effects, severe adverse events, and drug discontinuation rates were comparable between Rebif and Avonex. In the Drug Effectiveness Review Project at Oregon Health Sciences University, Rebif and Beta Seron were compared. In an effort to compare Rebif and Beta Seron, the DERP report reviewed 2 studies, neither of which found a significant difference in efficacy. However, the document states that Rebif had superior tolerability as measured by fewer injection site reactions, fewer flu-like symptoms, and less depression when compared to Beta Seron. Finally, Rebif is the only DMD with 2 FDA approved dosages, both of which are indicated for delaying confirmed progression and disability as measured by EDSS. This gives Rebif the greatest dosage flexibility among the DMDs. Rebif's efficacy, safety, tolerability, and outstanding patient support services and product enhancement services make it an excellent choice for MS. For this reason, she is requesting that Utah Medicaid Pharmacy Services P&T Committee place Rebif on the Utah Medicaid PDL.

Dr. Robert Martin of Bayer addressed the Committee. Bayer believes in the open access policy for MS agents. He was going to read the FDA labeled indications for Beta Seron, but that has already been covered. He would like to mention that the study that gained the approval for the CIS or early treatment indication, the BENEFIT trial, (stands for Beta Seron in Newly Emerging Multiple Sclerosis For Initial Treatment Study) was first published in 2006, and is an ongoing study. Beta Seron is the only high-dose high-frequency beta interferon that is approved for use in the early stages. In this BENEFIT trial, Beta Seron significantly delayed progression from the first single clinical demyelinating event to the time when there was evidence of clinically definite multiple sclerosis. The proportional hazard regression analysis showed a 50% reduction in the risk of progression to clinically definite MS in 2 years. The 5 year data was just presented at the Eckert Meeting in Montreal two months ago. The BENEFIT results at 5 years continue to demonstrate an advantage to patients started immediately on Beta Seron compared with the patients who received delayed treatment, specifically in the outcome of progression to clinically

definite multiple sclerosis, McDonald MS, as well as cognitive abilities. The BENEFIT study with Beta Seron is the only clinical trial with DMDs in MS that is prospective, and intention to treat, and now gone for 5 years in duration. The quality of this study and Bayer's commitment to do high-quality clinical research has generated new knowledge in the pathogenesis and treatment of MS. To date, Beta Seron has the longest evaluation period of any interferon beta in multiple sclerosis.

Dr. John Steffens, M.D. addressed the Committee. He advocated for equal access. Like Dr. Foley stated, it is quite a heterogeneous disease. One never knows which agent will work for a patient. Clinically, one of the deciding factors is all of the comorbidities. That plays a big role in selecting the first agent. In his practice, 40% of his patients end up switching their therapy at some point. Of those 50-60% do it within the first 18 months. If a switch is needed, he usually switches to a different drug class. If an interferon is needed, he will start with a high-dose interferon.

The Committee asked if there is a better improvement of one interferon versus another in terms of adverse effects causing noncompliance or stopping treatment. Dr. Steffens stated that this is not a problem in his practice, because he spends a great deal of time on education. In 90% of cases, he can talk a patient through an adverse event. He has had to stop a few people due to liver issues, but in most cases he finds that education deals with all of the issues.

Dr. Alison McReynolds, Scientific Manager with Teva Neuroscience, addressed the Committee about Copaxone. She recommends that patients have equal access to all therapies. Treatment early on is very important, as Dr. Foley indicated, and can really change the course of the disease. Even if a patient fails on one therapy, it does not mean that the patient is going to be refractory when switching to other therapies, particularly if they involve a different mechanism of action. Copaxone has a unique mechanism of action in that it shifts the immune response to be anti-inflammatory in nature rather than suppressing it. This specifically allows important immune functions to continue, while blocking disease activity in the site. Copaxone is the only drug with prospectively collected long-term data that now goes out to 15 years. In addition to telling us that 90% of patients will still be ambulatory in 15 years, it shows that Copaxone is very safe. Recent evidence has shown that there is great similarity in terms of efficacy between interferons and Copaxone. Recent studies have shown that Copaxone is effective as well in clinically isolated syndrome. A recent study has shown a 45% reduction in conversion to clinically definite MS, and the study had to be halted at 80% completion due to the ethical issues involved in keeping patients on placebo. With respect to safety, Copaxone is the only Pregnancy Category B drug, is not associated with flu-like syndrome or neutralizing antibodies. The only safety issues seen with it are injection site reactions, and an idiosyncratic post-injection reaction that results in long term sequilae. In addition, patients can take advantage of Teva's Shared Solutions program, which will allow patients to be more adherent. This can include everything from going in and answering questions to home nursing visits to help with the medication. Overall, Copaxone has shown equal efficacy with the interferons over the short term. Long term data suggests that the efficacy is extended over time. It has great safety data. Imaging markers have shown that in addition to what it being looked at clinically, no difference is seen between Beta Seron and Copaxone with respect to imaging markers. Smaller studies have shown effects of Copaxone on brain atrophy over time directly compare to some

of the interferons or are superior over the course of 5 years.

Karen Gunning stated that the Committee has received 6 letters that are remarkably similar seeking coverage of Rebif, and one letter seeking open access for all agents.

Dr. Beckwith stated that the Oregon review specifically did not include studies that evaluated MRI endpoints. They felt that this was a surrogate marker of the clinical outcome of the disease.

Duane Parke stated that the youngest person on Medicaid receiving an MS drug is age 14, and the vast majority of the patients on these drugs are women.

Dr. Ward stated that it is clear that this is a heterogeneous group in when a prescriber would want to use a particular agent, the side effects, and how it is dosed. If the Committee goes back to the singles small key question that they are to consider, if the agents are equally efficacious and safe, on that small question he would still have to say no. It is much more cloudy, but there is no evidence that any one agent is clinically superior and should be included to the exclusion of all others. Still, while it is obvious that a clinician needs to be able to choose different agents when a patient doesn't respond to one, it is not unreasonable to direct them to one agent first if that one agent could be made less expensive. Still, the physician would have the option to switch to any one of the other products if he were to indicate that it is medically necessary on the prescription. As far as a recommendation to Medicaid, he felt that he would have to recommend that they are equally safe and efficacious, even though they are a more heterogeneous group than usual.

Karen Gunning stated that she had the same initial reaction as Dr. Ward, when she first looked at the class. She understands that this is not a heterogeneous group. She did not hear from any clinicians that there is any one drug that stands out far above the rest. One of the issues with open access is that there is open access on the Utah Medicaid PDL, since there is no barrier per se, other than the requirement of writing "Medically necessary – Dispense as written" on the prescription. Looking at the drugs, there may be instances where glatiramer is used and interferons would not be used. It would seem logical to have at least have the glatiramer included because it is in a difficult class, but between the interferons it is difficult to tell.

Duane suggested that an Amber Sheet article about preferred agents be sent out. Karen felt that this should always be done.

The Committee felt that it would be reasonable to request that someone start on a particular agent, but that it would be inappropriate to suggest that someone switch from a therapy that they have been stabilized on.

Koby Taylor asked how grandfathering would be handled. He stated that he has had 3 patients not be able to receive medications due to programming issues within the last week, even when they have had prescriptions with "Medically Necessary – Dispense as written" written on their prescriptions. Karen Gunning stated that she did not feel that it was within the purview of the Committee to solve that.

Duane made a motion stating that he found that none of the DMDs had significant differences in safety or efficacy. Jerome Wohleb seconded the motion. Dr. Ward asked if a line should be added to the motion that the PDL should include both glatiramer and an interferon. Dr. Beckwith suggested that Duane's original motion be considered, and that Dr. Ward's suggestion be considered as a separate motion. The motion passed with unanimous votes by Koby Taylor, Karen Gunning, Dr. Ward, Kort DeLost, Dr. Harris, Dr. Weeks, Dr. Rondina, and Jerome Wohleb.

Dr. Weeks stated that he had concerns about trying to direct providers to one or two agents, even with open access via medical necessity for the concerns that Dr. Taylor raised. Even though it may not be within the purview of the Committee, he has concerns that trying to have a preferred agent from a patient access standpoint. Karen explained that the Committee doesn't have the power to choose a preferred drug, but that they could do a motion making a recommendation on efficacy and safety. Dr. Weeks made a motion that he would not encourage a PDL in this class due to the concerns about the heterogeneity of MS and the treatments. He did not feel comfortable enough with the disease process to recommend a PDL.

There was no second to the motion, but Karen Gunning stated that Utah Medicaid should consider the deliberations of the Committee when choosing a preferred drug. She also addressed the neurologists in the audience and stated that in looking at the claims data, she was surprised to find that adherence among Medicaid patients appears to be quite poor. It would be interesting to do a study to see why patients discontinue or fail to refill their medications. On the usage chart that was provided to the Committee, it looks like patients receive about 6 prescriptions in a 12 month period. This may be due to changes in eligibility, but it is striking that patients do not seem to receive adequate amounts of medication.

5. Niacin/Statin Combinations: Dr. Erin Fox addressed the Committee. There are two combination statin/niacin extended release combinations. Advicor is lovastatin plus niacin extended release, and Simcor is simvastatin plus niacin extended release. These agents are both labeled to lower the lipid profile in patients with primary hypercholesterimia, mixed dyslipidemia, or trigliceridemia. Statin + niacin combinations may be useful in patients who are already on niacin therapy and need the extra additional LDL lowering or for patients who are on statin therapy an need additional triglyceride lowering or an increase in HDL to meet their treatment goals. In developing this review, they first looked for head-to-head trials comparing the two agents and they were not able to find any trials. They also looked for any trials evaluating improvements in mortality with either of the specific combination products, and they were also unable to locate any of those trials. Little data are available. They then focused on how much these products improve lipid profile, and did not include trials without any control groups in the analysis. They also looked as safety data.

   There is one trial that compares Advicor to either simvastatin or atorvastatin monotherapy. After 4 months of therapy, the atorvastatin was more effective for lowering LDL compared to simvastatin monotherapy or Advicor. Advicor was more effective for increasing HDL compared to the atorvastatin monotherapy or simvastatin monotherapy. There are also two clinical trials that compare Simcor to simvastatin monotherapy. Simcor has not shown any additional decrease in LDL

lowering compared to the simvastatin monotherapy, but did increase HDL cholesterol more than simvastatin alone.

As far as side effects with these agents, flushing is the most common adverse event occurring in 53-83% of all patients. Interestingly, in clinical trials only 6-8% of patients discontinued therapy because of this. Overall, the discontinuation rates were 14-19%. Other common adverse effects include headache, pruiritus, nausea, or diarrhea. Myopathy and rhabdomyelosis are possible. These agents are impacted by potent inhibitors of CYP 3A4, so there are a lot of drug interactions that are fairly similar between both agents. These drugs need to be titrated carefully because of the extended release niacin component, for patient tolerability. Doses greater than 2000mg of niacin with greater than either 40mg of simvastatin or lovastatin are not recommended.

In summary, many patients on statin or niacin therapy may require combination therapy to achieve their triglyceride, LDL, or HDL goals. These medications are available separately, but the combination products may be appropriate if they are at least as cost effective as the individual components separately.

Pam Sardo of Abbott addressed the Committee. Trials using statins to lower LDL have consistently shown reductions that have been discussed earlier. However, despite LDL lowering, a residual coronary artery disease risk does remain, some of which may be modifiable. While guidelines have determined an appropriate target for lowering LDL, the ATP3 guidelines also mention non-HDL as a secondary target for therapy. Therefore, as was previously discussed, Simcor can be used as an adjunct to diet for patients requiring modifications of the lipid profile that were discussed. In the studies, there was a greater reduction in the non-HDL parameters than in the patients with simvastatin monotherapy. Simcor is also contraindicated in the patients where the single agents would be contraindicated, such as in active liver disease, pregnancy, or peptic ulcer disease.

Dr. Elliot Brinton addressed the Committee. He is the chief of the metabolism section of cardiovascular genetics at the University of Utah. He is a Board Certified Clinical Lipidologist. He would like to speak in favor of Simcor as being on the PDL. It is true that there are no head-to-head comparisons with Simcor and Advicor, but there are a number of comparisons that have looked at lovastatin and simvastatin. Generally speaking, simvastatin is more effective in LDL lowering, and males have slightly better efficacy as far as HDL cholesterol and triglycerides are concerned. Simcor is a generally a better agent than Advicor. Although he has some patients on Advicor that are doing well, he will generally being new starts on Simcor. The only reason he would not use Simcor is if someone insisted in having a "natural" product, because lovastatin occurs in nature. Fixed dose combinations offer an advantage as well. Studies have shown that reducing the pill count for patients is helpful. It also helps the physician or clinician to have to write fewer prescriptions. In terms of the dosing, it is straightforward, and there is some advantage in cost. For these reasons, it is preferable to use a fixed dose combination for these medications that will be long term or life-long. Simvastatin is the single most widely used statin, and niacin is the most widely used agent for raising HDL. The American Heart Association and the National Lipid Association have both strongly endorsed the use of prescription niacin over dietary supplement niacin. Extended release prescription niacin is preferred for

many reasons in the medical community, including the reason that the prescription niacin is regulated. There have been a number of studies looking at extended release niacin in the dietary supplement form that have revealed problems with hepatotoxicity. There are a number of study data looking at Simcor's ability to treat not only to the LDL goal, but also to the non-HDL goal. There are also HDL and triglyceride targets, which were also mentioned. Generally speaking, about ¾ of new patients can get to their target in all 4 cases, which is better than any single agent or any other fixed dose combination. Mention was made of a lack of studies showing artherosclerosis reduction with a fixed dose combination. There are no studies to date that show that, but there are studies with each individual agent that have been shown to reduce cardiovascular risk and cardiovascular events. There are some small studies that have shown that the combination of the two agents, though not in a fixed dose, showed a event reduction and arthero reduction in that particular combination. There are two large ongoing trials that are looking at these combinations. They have not been stopped for safety concerns, and will probably give confirmation within the next few years of what has been seen in the smaller trials about the additive arthero reduction and additive cardiovascular risk reduction with the two agents added together.

Dr. Ward stated that the components of these agents are available with preferred status. None of the evidence presented has suggested that these agents offer any clinical benefit over writing separate prescriptions for the component products. From a clinical point of view, there is no reason to give these agents preferred status over what is already available.

Karen Gunning stated that the only concern that she has, which would be for the DUR Board to address, is that she has seen several patients on a combination product plus a statin. This presents a safety issue, and should be hard edited with both the niacin product and the statin product.

Dr. Ward agreed that it is sometimes difficult for patients who are struggling to understand what they are already on to understand this new drug name and understand that there are two agents in it.

Duane Parked asked Dr. Brinton to comment on the niacin sustained release versus the OTC supplements. Dr. Brinton stated that niacin supplements are not over-the-counter. OTC products have the same safety regulations on them as prescription products, except the requirement for a prescription and pharmacist involvement. There is quite a large difference between dietary supplements and prescription products. There are actually two prescription products, one of which is extended release and one of which is immediate release. Then there is a host of dietary supplement products. Even though there is an inclination to save money with the dietary supplement products, both the American Heart Association and the National Lipid Association have come out fairly strongly against the use of dietary supplements due to the general lack of regulation and the confusion on the part of the patient who may not get the correct thing at the grocery store. With a prescription, there is some assurance that the pharmacist will give the correct drug to the patient. Published studies have also consistently shown issues with safety of dietary supplements as compared to the better tolerated prescription sustained release counterpart. As far as the issue of fixed dose combinations versus two –pill

combinations, there are a number of studies that have shown better long term compliance with a reduction in pill count. Going to a combination product does do that. Compliance is a big issue. Problems with long term compliance are probably the biggest issue with these drugs.

Dr. Sardo added that the FDA has posted a safety advisory for problems with over the counter niacin supplements, and offered to provide a link to the information.

Dr. Ward made a motion that the fixed dose combination niacin/statin products do not provide superior clinical outcomes when compared to the single prescription agents. Medicaid should choose which agents to include based on cost. Kort DeLost seconded the motion. The motion passed with unanimous votes by Koby Taylor, Karen Gunning, Dr. Ward, Kort DeLost, Dr. Harris, Dr. Weeks, Dr. Rondina, and Jerome Wohleb.

Next Meeting Set for Thursday, December 18, 2008
Meeting Adjourned.

Minutes prepared by Jennifer Zeleny